

## Mutations in Spliceosomal Genes PPIL1 and PRP17 Cause Neurodegenerative Pontocerebellar Hypoplasia with Microcephaly.

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### Public Summary:

Autosomal-recessive cerebellar hypoplasia and ataxia constitute a group of heterogeneous brain disorders caused by disruption of several fundamental cellular processes. Here, we identified 10 families showing a neurodegenerative condition involving pontocerebellar hypoplasia with microcephaly (PCHM). Patients harbored biallelic mutations in genes encoding the spliceosome components Peptidyl-Prolyl Isomerase Like-1 (PPIL1) or Pre-RNA Processing-17 (PRP17). Mouse knockouts of either gene were lethal in early embryogenesis, whereas PPIL1 patient mutation knockin mice showed neuron-specific apoptosis. Loss of either protein affected splicing integrity, predominantly affecting short and high GC-content introns and genes involved in brain disorders. PPIL1 and PRP17 form an active isomerase-substrate interaction, but we found that isomerase activity is not critical for function. Thus, we establish disrupted splicing integrity and "major spliceosome-opathies" as a new mechanism underlying PCHM and neurodegeneration and uncover a non-enzymatic function of a spliceosomal proline isomerase.

### Scientific Abstract:

Autosomal-recessive cerebellar hypoplasia and ataxia constitute a group of heterogeneous brain disorders caused by disruption of several fundamental cellular processes. Here, we identified 10 families showing a neurodegenerative condition involving pontocerebellar hypoplasia with microcephaly (PCHM). Patients harbored biallelic mutations in genes encoding the spliceosome components Peptidyl-Prolyl Isomerase Like-1 (PPIL1) or Pre-RNA Processing-17 (PRP17). Mouse knockouts of either gene were lethal in early embryogenesis, whereas PPIL1 patient mutation knockin mice showed neuron-specific apoptosis. Loss of either protein affected splicing integrity, predominantly affecting short and high GC-content introns and genes involved in brain disorders. PPIL1 and PRP17 form an active isomerase-substrate interaction, but we found that isomerase activity is not critical for function. Thus, we establish disrupted splicing integrity and "major spliceosome-opathies" as a new mechanism underlying PCHM and neurodegeneration and uncover a non-enzymatic function of a spliceosomal proline isomerase.

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